## REMARKS

Upon entry of the present amendment, claims 1-13 and 48-71 are pending in the application. Claims 1-4 and 11-13 have been amended, and claims 48-71 have been added. The present amendments are fully supported by the specification and the claims as originally filed. For example, support for the amendments to claims 1, 2 and 11, as well as new claims 48-71, is found at least at page 4, lines 15-21 and at page 13, lines 27-29. Support for the amendments to claims 3, 4, 12 and 13 is found at least at page 3, lines 22-28. Accordingly, no new matter has been added by this filing.

### Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 3-4 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. In particular, the Examiner has indicated that the ranges recited by claims 3 and 4 are inconsistent with the reduced folate to cobalamin ratio limitation recited by independent claim 2, *i.e.*, 125:1.

Claims 3 and 4 have been amended to recite ranges of reduced folate and cobalamin, wherein the upper and lower end of each recited range falls within the 125:1 ratio recited by independent claim 2. Accordingly, Applicants submit that claims 3 and 4, as amended, are clear, definite and consistent with the limitations recited by independent claim 2. As such, withdrawal of this rejection is requested.

### Rejections under 35 U.S.C. § 103

*Claims 1-5, 9 and 10*

Claims 1-5, 9 and 10 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,011,040 by Muller *et al.* ("Muller"). According to the Examiner, "those of ordinary skill in the art would have been readily optimized effective dosage in light of Muller who teaches the range of amounts of reduced folate compound and cobalamin (vitamin B12) in said composition." (Office Action, page 4).

Claim 1, as amended, is directed to a composition that includes a reduced folate compound and a cobalamin compound in amounts sufficient to exert a chondroprotective effect, wherein the reduced folate is selected from the group consisting of 5-formimino-(6S)-tetrahydrofolic acid and 5-formimino-(6R,S)-tetrahydrofolic acid, wherein the ratio of the reduced folate compound and the cobalamin is 125:1, and wherein the composition further

includes a non-steroidal anti-inflammatory drug (NSAID), a steroid, an immunosuppressant, a cyclooxygenase inhibitor or a combination thereof.

Amended claim 2 recites a composition that includes a reduced folate compound and a cobalamin compound, wherein the ratio of the reduced folate compound and the cobalamin is 125:1, and wherein the composition further includes a non-steroidal anti-inflammatory drug (NSAID), a steroid, an immunosuppressant, a cyclooxygenase inhibitor or a combination thereof.

Thus, the claimed compositions contain a reduced folate compound and a cobalamin compound such that the reduced folate compound and the cobalamin are present in a ratio of 125:1. Muller fails to describe or suggest a composition that includes reduced folate and cobalamin in a ratio of 125:1. In the only Example that describes a pharmaceutical preparation that contains both a reduced folate compound (5-methyl-(6S)-tetrahydrofolic acid) and a cobalamin compound (vitamin $B_{12}$), the ratio of reduced folate to cobalamin is 0.4 mg of 5-methyl-(6S)-tetrahydrofolic acid to 0.002 mg of vitamin $B_{12}$, *i.e.*, a ratio of 200:1 (*See* Muller, Example 10 at col. 5, lines 9-19).

Moreover, the claims have now been amended to include a non-steroidal anti-inflammatory drug (NSAID), a steroid, an immunosuppressant, a cyclooxygenase inhibitor or a combination thereof. Muller fails to teach or suggest compositions that contain any of these agents. Accordingly, the amended claims are not obvious in view of the teachings of the Muller reference. Applicants, therefore, request that this rejection be withdrawn.

*Claim 6-8 and 11-13*

Claims 6-8 and 11-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Muller reference in view of International Publication No. WO 98/19690 by Smith *et al.* ("Smith"). According to the Examiner, "one having ordinary skill in the art would have expected as taught by Smith that the use of secondary ingredient such as betaine in composition containing folic acid, folate or folate derivatives and vitamin B12 is old and well known." (Office Action, page 4).

Claim 6-8 depend, directly or indirectly from claim 2, which has been amended to recite a composition that includes a reduced folate compound and a cobalamin compound, wherein the ratio of the reduced folate compound and the cobalamin is 125:1, and wherein the composition further includes a non-steroidal anti-inflammatory drug (NSAID), a steroid, an immunosuppressant, a cyclooxygenase inhibitor or a combination thereof.

Claim 11, as amended is directed to a composition that contains folic acid or a reduced folate compound, a cobalamin compound, and betaine in amounts sufficient to exert a chondroprotective effect, wherein the folic acid or reduced folate compound comprises 150-1000 mg of the composition, and wherein the ratio of the reduced folate compound and the cobalamin is 125:1, and wherein the composition further includes a non-steroidal anti-inflammatory drug (NSAID), a steroid, an immunosuppressant, a cyclooxygenase inhibitor or a combination thereof.

As described above, the Muller reference does not teach or suggest compositions that contain a non-steroidal anti-inflammatory drug (NSAID), a steroid, an immunosuppressant, a cyclooxygenase inhibitor or a combination thereof. The Smith reference fails to remedy the deficiencies in the teachings of Muller. In particular, the Smith reference does not disclose or suggest compositions that contain folic acid or a reduced folate compound, a cobalamin compound, betaine, and one or more additional agents selected from a non-steroidal anti-inflammatory drug (NSAID), a steroid, an immunosuppressant, a cyclooxygenase inhibitor or a combination thereof. There is no teaching or suggestion in the cited references, alone or in combination, that would motivate the skilled artisan to include any of the claimed additional agents in the compositions described therein.

Accordingly, the claimed compositions are not obvious over the Muller and Smith references, either alone or in combination. As such, this rejection should be withdrawn.

## CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact any of the undersigned at the telephone number provided below. The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No.21629-004.

Respectfully submitted,

IABeattie

Ingrid A. Beattie, Reg. No. 42,306
Attorney for Applicant
MINTZ, LEVIN, COHN, FERRIS
GLOVSKY and POPEO, P.C.
Tel: (617) 542-6000
Fax: (617) 542-2241
**Customer No. 30623**

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